

70. (Amended) A host cell comprising at least a first nucleotide sequence that encodes a mammalian methylthioadenosine phosphorylase polypeptide comprising the amino acid sequence of SEQ ID NO:2.

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71 (Amended) The host cell of claim 70, wherein said nucleotide sequence comprises the nucleic acid sequence of from about nucleotide 122 to nucleotide 970 of SEQ ID NO:1.

Please delete claims 95-96.

### **RESPONSE TO OFFICE ACTION**

#### **A. State of the Claims**

At the time of the Action, claims 39-96 were pending. No claims have been added and claims 95 and 96 have been deleted. Claims 54, 57, 67, 68, 70 and 71 have been amended without acquiescence or prejudice to clarify the claimed invention. Therefore, claims 39-94 are currently pending. A clean copy of the pending claims after the amendments are attached hereto in Appendix B.

#### **B. The 35 U.S.C. § 102(b) Rejections Over Kamb et al. are Overcome.**

Claims 39-50, 52-57, 59, 60, 67-76, 78, 80-83, 88-94 are rejected under 35 U.S.C. § 102(b) as anticipated by Kamb et al. Kamb et al. is said to teach isolated nucleotides containing the tumor suppressor gene MTS1 which maps to 9p21-22 and is tightly linked to MTAP. The cosmid of Kamb et al. is said to comprise the sequence of SEQ ID NO. 1 and, therefore, the Action suggests that the nucleotide of Kamb et al. comprises at least 21, 30, 40 or all contiguous bases from nucleotides 122-970 of SEQ ID NO 1. The Action states that the nucleotide sequence

of Kamb et al. inherently meets the limitations of claims 45 and 46. Kamb et al. is further said to teach a method for detecting a nucleic acid comprising a sequence encoding MTAP by hybridization by a probe comprising at least 21 bases of SEQ ID NO 1.

Applicant respectfully traverses these rejections.

Kamb et al. appears to describe work aimed at searching for candidate tumor suppressor genes. During this search, parts of cosmid C5 were sequenced and identified as the MTS1 and MTS2 genes. The 9p21 region contains multiple genes in addition to MTS1 and MTS2. Kamp et al. report DNA sequences for the two closely related genes MTS1 and MTS2, but do not identify, isolate or sequence a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1 of the present invention. The entire cosmid C5 was not sequenced. Even if the cosmid C5 comprised MTAP, Kamb et al. did not disclose a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1, or a nucleotide comprising a sequence region that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

As is well established by the courts, conception of a gene requires isolation of the gene, or defining the gene so as to distinguish it from other materials, as well as how to make it. *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) ("When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred (i.e., until after the gene has been isolated").

Kamb et al. do not disclose a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Prior to the disclosure of SEQ ID NO:1 by Applicant, there was no understanding of where the sequence encoding a methylthioadenosine phosphorylase polypeptide was located. Thus, Applicant asserts that Kamb et al do not each every limitation of the claims (*Verdegaa*

*Bros. v. Union Oil Co. of California* 814 F.2d 628, USPQ2d (BNA) 1051, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d (BNA 1913)) as a consequence, the anticipation rejections are overcome. Applicant respectfully requests the withdrawal of these rejections.

**C. The 35 U.S.C. § 102(b) Rejections Over Nobori et al. are Overcome.**

Claims 54-66, 74-75, 77-83 and 88-94 are said to be anticipated by or, in the alternative, obvious over Nobori et al. (1994), which is said to teach that methylthioadenosine phosphorylase cDNA was isolated and a 2-kilobase fragment was found to contain the 3' end of the *MTAP* gene. Nobori et al. (1994) is said to have used this sequence as a probe for chromosome walking. The Action argues that, although Nobori et al. (1994) only disclose a 3' fragment of the human *MTAP* gene, the claims as written read on nucleotides containing fragments of the *MTAP* gene as small as 10 bases.

Applicant asserts that the Nobori et al. is not enabling. Therefore, the 102(b) rejection should be withdrawn. Applicant refers the Examiner to *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed Cir. 1985) which states a disclosure will not suffice as prior art if it was not enabling. Under 35 U. S. C. 102b, prior art must sufficiently describe the claimed invention to have placed the public in possession of it; such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. *In re LeGrice*, 301 F.2d 939, 133 USPQ 365, 371 (CCPA 1962).

The Nobori et al. (1994) publication reports the sequence analysis of the CDK4I coding region of a lymphoblastoid cell line and speculates that the CDK4 inhibitor is a strong candidate for a melanoma susceptibility gene. A 19-kb  $\lambda$ -phage clone designated 10B1 was subcloned and a fragment of CDK4 inhibitor gene identified. The subclone was said to contain an open base

reading frame with a sequence identical to the 3' region of a previously reported CDK4 inhibitor. The Nobori et al. (1994) reference showed a physical map of chromosome 9p21 between two gene loci (i.e., MTAP and IFN- $\beta$ ). However, the physical map shown is incorrect, as confirmed by Nobori et al. in *Proc. Natl. Acad. Sci. USA* 3:6203-6208 (1996). Nobori et al. (1996) states on pages 6206 to 6207 that the preliminary Southern blotting experiments lead them to believe that that *MTAP* was centromeric to *p16*, but detailed analysis of YAC clones and separation of DNA in pulse-field gels refuted this supposition. Thus, the correct gene order on human chromosome 9p is *p15—p16—MTAP—IFN $\alpha$*  from centromeric to telomeric.

Therefore, the Nobori et al. (1994) reference discloses the wrong map of cDNA. This reference would lead those of ordinary skill in the art to look in the wrong place for a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. In view of the disclosure of the wrong map of cDNA, Applicant refers the Examiner to *In re Wiggins*, 488 F.2d 538, 179 USPQ (CCPA) 1973) and *In re Sheppard*, 339 F.2d 238, 144 USPQ 42 (CCPA 1964). In both of these cases, the references were deemed insufficient, because attempts to prepare the claimed compounds were unsuccessful. Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling. In this case, failure of Nobori et al. (1994) to develop a correct physical cDNA map would lead to further failures of those of skill in the art trying to utilize the nonenabling publication of Nobori et al. (1994) to identify and isolate the *MTAP* gene.

However, the Action contends that the fact that Nobori et al. do not teach the nucleotide sequence of the 3' end of the *MTAP* gene does not obviate the fact that they were in possession of a nucleic acid sequence which encodes an MTAP polypeptide fragment.

Applicant respectfully traverses.

Nobori et al. (1994) had only a small fragment of the *MTAP* gene, and did not disclose the sequence of even that small fragment. Characterization, isolation and sequencing of a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1 were not disclosed by Nobori et al. (1994) and probes from the 3' end of the *MTAP* gene were, in fact, employed to study absence or rearrangement of the CDK4 inhibitor gene in malignant cell lines, not to isolate, sequence and characterize a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Thus, the Nobori et al. (1994) was nonenabling due to the incorrect cDNA sequence and did not sufficiently disclose the claimed invention to have placed the public in possession of it. *Id.* Applicant asserts that the mere fact that Nobori et al. (1994) used a probe containing the 3' end of the *MTAP* gene does not inherently establish that Nobori et al. had in their possession the nucleic acid sequence of SEQ ID NO:1 capable of encoding an mRNA transcript that could be translated into a functional MTAP protein.

Applicant again directs the Examiner's attention to *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991), which confirms that conception of a gene requires isolation of the gene, or defining the gene so as to distinguish it from other materials, as well as how to make it. Applicant concludes that Nobori et al. do not disclose a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1 because the nucleic acid sequence from SEQ ID NO:1 had not been isolated and sequenced, nor is there mention of kits or methods of use for a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. The anticipation rejections over Nobori et al. (1994) are overcome. Applicant therefore submits that these rejections should be withdrawn.

**D. The 35 U.S.C. § 103(a) Rejections are Overcome.**

**1. Claims 39-42, 45-66, 74-75, 77-83 and 88-94 are nonobvious**

Claims 39-42, 45-66, 74-75, 77-83 and 88-94 are said to be obvious over Nobori et al. (1994). Nobori is said to teach that methylthioadenosine phosphorylase cDNA was isolated and a 2-kilobase fragment was found to contain the 3' end of the *MTAP* gene. Nobori et al. (1994) is said to have used this sequence as a probe for chromosome walking. The Action argues that, although Nobori et al. (1994) only disclose a 3' fragment of the human *MTAP* gene, the claims as written read on nucleotides containing fragments of the *MTAP* gene as small as 10 bases. The Action asserts that claims limited to a nucleotide consisting of the *MTAP* gene would have been *prima facie* obvious over Nobori et al. (1994) because Nobori et al. (1994) discloses a highly specific probe for isolating the complete coding sequence for the *MTAP* gene. According to the Action, the ordinary artisan would be highly motivated to obtain the remainder of the *MTAP* gene.

Applicant traverses.

As stated above regarding the 35 U.S.C. § 102(b) rejection, the Nobori et al. (1994) publication reports that a 19-kb  $\lambda$ -phage clone designated 10B1 was subcloned and a fragment of CDK4 inhibitor gene identified. The subclone was said to contain an open base reading frame with a sequence identical to the 3' region of a previously reported CDK4 inhibitor. The Nobori et al. (1994) reference showed a physical map of chromosome 9p21 between two gene loci (i.e., *MTAP* and *IFN- $\beta$* ). However, the physical map shown is incorrect, as confirmed by Nobori et al. in *Proc. Natl. Acad. Sci. USA* 3:6203-6208 (1996). The Nobori et al. (1996) reference discloses

at page 6207 that the correct gene order on human chromosome 9p is *p15—p16—MTAP—IFNA* from centromeric to telomeric.

Thus, the Nobori et al. (1994) references discloses the wrong map of cDNA. This reference would lead those of ordinary skill in the art to look in the wrong place for a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Norbori et al. (1994) consequently teaches away from the present invention, rendering the present invention nonobvious. Proceeding contrary to the accepted wisdom of the prior art is strong evidence of nonobviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983); *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986). An invention's contradicting the teachings and express expectations of the prior art has long been a criterion of patentability. *Racal-Vadic, Inc. v. Universal Data Systems*, 207 U.S.P.Q. 902 (Ala. 1980).

The Action contends that Nobori et al. (1994) discloses a highly specific probe for isolating the complete coding sequence for the *MTAP* gene, and that the ordinary artisan would be highly motivated to obtain the remainder of the *MTAP* gene. The Action mistakenly assumes that a small portion of the gene used as a probe would motivate one of skill to isolate the entire gene. The Patent Office appears to assert it has more knowledge than the skilled artisans and thus, it is substituting its judgment for that of an established expert in the art. This is improper. *In re Zeidler*, 682 F.2d.961, 966-967 (Fed. Cir. 1982). Yet further, the Action is proposing a fishing expedition for those of skill in the art when there is no motivation to isolate the entire gene that was used merely for a probe.

However, at best, in view of Nobori et al. (1994), one skilled in the art might find it obvious to try to obtain the remainder of nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. This is not the standard of 35 U.S.C. § 103. *In re Geiger*, 815 F.2d 686 (Fed.

Cir. 1987). “‘Obvious to try’ has long been held not to constitute obviousness.” *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) (citing *In re O’Farrell*, 853 F.2d 894 (Fed. Cir. 1988)). An “obvious-to-try” situation exists when a general disclosure may pique the scientist’s curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943 (Fed. Cir. 1990). A particular result, such as the sequence of a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1, is not made obvious by a general incentive, nor by the existence of techniques by which those efforts can be carried out. *In re Deuel*, 51 F.3d at 1559. “The fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious.” *Id.* Yet further, Applicant reminds the Examiner that the existence of a general method of isolating DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993).

Since that the map disclosed by Nobori et al. (1994) was incorrect and that the reference did not disclose the sequence of any part of a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1, let alone isolate and characterize a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1, Nobori et al. (1994) does not contain sufficient teaching to render the present invention *prima facie* obvious. The minimal disclosure of Nobori et al would result in undue experimentation by those of skill in the art if they were motivated to try to isolated the sequence of SEQ ID NO:1. Yet further, Applicant reminds the Examiner that the teaching or suggestion to make the claimed invention and the reasonable expectation of success must be



found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). With the lack of teaching or suggestion to isolate the gene nor the reasonable expectation of success, Applicant asserts that Nobori et al do not meet the basic requirements of a *prima facie* case of obvious.

## **2. Claims 84-87 are nonobvious**

Claims 84-87 are rejected as being obvious over Nobori et al. (1994) which is said to teach the association of the 9p21-22 region with cancers due to its frequent deletion in patients with various cancers and teach that this region was suspected to contain a number of tumor suppressor genes. The Action argues that it would have been *prima facie* obvious to one of ordinary skill in the art to have packaged the nucleotides and vectors taught by Nobori et al. (1994) with detection reagents in a kit in order to achieve the expected benefit of providing probes to use in a method of screening for deletions of the 9p21-22 region as suggested by Nobori et al. (1994) in a convenient form.

Applicant traverses.

Claims 84-87 of the present invention claim a detection kit comprising a first nucleic acid segment comprising at least 21 contiguous nucleotides of SEQ ID NO:1. Nobori et al. (1994) nor does not disclose any contiguous nucleotide of SEQ ID NO:1. Nobori et al. (1994) discloses merely a 3' fragment of the human *MTAP* gene, and none of the sequence of the gene. Further, Nobori et al. (1994) discloses the wrong map of cDNA, and would lead those of ordinary skill in the art to look in the wrong place for a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Nobori et al. (1994) consequently teaches away from the present invention, rendering the present invention nonobvious. As stated above, proceeding contrary to the accepted wisdom of the prior art is strong evidence of nonobviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*,

721 F.2d 1540 (Fed. Cir. 1983); *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986). An invention's contradicting the teachings and express expectations of the prior art has long been a criterion of patentability. *Rucal-Vadic, Inc. v. Universal Data Systems*, 207 U.S.P.Q. 902 (Ala. 1980).

For the reasons above, withdrawal of the § 103(a) rejections is proper.

**F. The 35 U.S.C. § 112, first paragraph, Rejections are Overcome.**

Claims 54-60, 67-76, and 88-94 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The Action states that the specification does not describe the 5' and 3' regulatory regions of the *MTAP* gene and that therefore have not fully described the *MTAP* gene.

Applicant respectfully traverses.

Applicant defines on page 10, line 5 of the specification, that the term "gene" is used for simplicity to refer to the functional protein or polypeptide. Yet further, in FIG. 3A and FIG. 3B, Applicant defines the nucleic acid sequence and the amino acid sequence of MTAP. Upon examination of FIG. 3A, one of skill in the art would be able to determine the transcriptional start site and the polyadenylation site. Thus, the two significant regulatory regions for *in vitro* expression located in the 5' and 3' untranslated regions are evident from FIG. 3A.

However, in order to advance the prosecution of this application, Applicant has amended the claims to replace "gene" with "nucleotide sequence". This amendment eliminates the Examiner's preconceived definition of gene and that all of the regulatory regions must be identified. In light of these amendments, Applicant respectfully request removal of the 112, first paragraph rejection.

The Action further contends that the claims encompass mammalian homologs of the human *MTAP* gene and that the specification is unclear if any other species are represented in the Northern blot of FIG. 13. Applicant refers the Examiner to page 21, line 6 and page 39, line 26. The Northern blot is an evolutionary blot (page 39, line 26) or zoo blot. One of skill in the art realizes that this blot would contain samples from a variety of evolutionary species. The lanes of the Northern blot are described on page 21, line 6, for example, the Northern blot included human cancer cell lines in addition to simian virus (SV40) and bacterium.

Yet further, claims 95-96 are said to be rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. In view of the amendments, Applicant respectfully requests that the 35 U.S.C. § 112, first paragraph rejection be removed.

#### **G. Conclusion**

Claims 39-96 are pending in this application. Applicant has attached a clean copy of the pending claims in this application after amendments for the Examiner's convenience. Claims 54, 57, 67, 68, 70 and 71 have been amended and claims 95-96 have been deleted to merely clarify the claimed invention. Therefore, these amendments do not narrow the scope of the claims within the meaning of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 586, 56 USPQ2d 1865, 1886 (Fed. Cir. 2000).

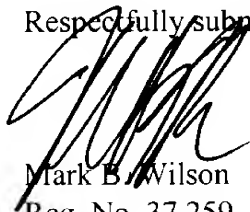
Applicant submits that none of the references cited by the action anticipates or renders obvious the subject matter disclosed and claimed in the present application. Applicant is the first to have isolated and sequenced a nucleotide comprising a nucleic acid sequence from SEQ ID

NO:1. The enzyme encoded by the gene had been previously known; however, only the general location of the *MTAP* gene was recognized. As noted by the court in *Amgen, Inc.*, "...conception has not been achieved until reduction to practice has occurred, *i.e.* until after the gene has been isolated." *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 Fed. 2d at 1206. None of the references had identified the structure or physical characteristics of the *MTAP* gene.

The Action's position appears to be that because a large piece of DNA that may contain the *MTAP* gene but which has not been sequenced and from which the *MTAP* gene has not been isolated, anticipates or renders obvious a nucleotide comprising a nucleic acid sequence from SEQ ID NO:1. This contradicts the position taken by the courts which have repeatedly emphasized that a gene is a chemical compound and that conception of chemical compounds require the definition of that compound (see *Okaa*, 849 F2d at 583, 7 U.S.P.Q. 2d at 1171, 1988).

Applicant intends this to be a complete response to the examiner's action and reconsideration of the application is respectfully requested. Should any further issues remain, the undersigned attorney respectfully requests a telephone call at (512) 418-3035.

Respectfully submitted,



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## Appendix A

### MARKED UP VERSION OF AMENDED CLAIMS

#### IN RESPONSE TO OA DATED 10/12/01

54. (Amended) A nucleic acid of from about 850 to about 10,000 nucleotides in length comprising a [gene] nucleotide sequence encoding a methylthioadenosine phosphorylase polypeptide, said polypeptide comprising a sequence region of at least about 10 contiguous residues from SEQ ID NO:2.
57. (Amended) The nucleic acid of claim 54, wherein said [gene] nucleotide sequence is operably linked to a heterologous promoter.
67. (Amended) A vector comprising at least a first [gene] nucleotide sequence that encodes a mammalian methylthioadenosine phosphorylase polypeptide comprising the amino acid sequence of SEQ ID NO:2.
68. (Amended) The vector of claim 67, wherein said [gene] nucleotide sequence comprises the nucleic acid sequence of SEQ ID NO:1.
70. (Amended) A host cell comprising at least a first [gene] nucleotide sequence that encodes a mammalian methylthioadenosine phosphorylase polypeptide comprising the amino acid sequence of SEQ ID NO:2.
71. (Amended) The host cell of claim 70, wherein said [gene] nucleotide sequence comprises the nucleic acid sequence of from about nucleotide 122 to nucleotide 970 of SEQ ID NO:1.